MEF2C-Directed Neurogenesis From Human Embryonic Stem Cells

Grant Award Details

MEF2C-Directed Neurogenesis From Human Embryonic Stem Cells

Grant Type: Comprehensive Grant

Grant Number: RC1-00125

Investigator:

Name:	Stuart Lipton
Institution:	Sanford-Burnham Medical Research Institute
Type:	PI

Disease Focus: Parkinson's Disease, Neurological Disorders, Stroke, Neurological Disorders

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: $2,832,000

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: NCE

View Report

Grant Application Details

Application Title: MEF2C-Directed Neurogenesis From Human Embryonic Stem Cells

Public Abstract: Understanding differentiation of human embryonic stem cells (hESCs) provides insight into early human development and will help directing hESC differentiation for future cell-based therapies of Parkinson's disease, stroke and other neurodegenerative conditions.

The PI's laboratory was the first to clone and characterize the transcription factor MEF2C, a protein that can direct the orchestra of genes to produce a particular type of cell, in this case a nerve cell (or neuron). We have demonstrated that MEF2C directs the differentiation of mouse ES cells into neurons and suppresses glial fate. MEF2C also helps keep new nerve cells alive, which is very helpful for their successful transplantation. However, little is known about the role of MEF2C in human neurogenesis, that is, its ability to direct hESC differentiation into neuronal lineages such as dopaminergic neurons to treat Parkinson's disease and its therapeutic potential to promote the generation of nerve cells in stem cell transplantation experiments. The goal of this application is to fill these gaps.

The co-PI's laboratory has recently developed a unique procedure for the efficient differentiation of hESCs into a uniform population of neural precursor cells (NPCs), which are progenitor cells that develop from embryonic stem cells and can form different kinds of mature cells in the nervous system. Here, we will investigate if MEF2C can instruct hESC-derived NPCs to differentiate into nerve cells, including dopaminergic nerve cells for Parkinson's disease or other types of neurons that are lost after a stroke. Moreover, we will transplant hESC-NPCs engineered with MEF2C to try to treat animal models of stroke and Parkinson's disease. We will characterize known and novel MEF2C target genes to identify critical components in the MEF2C transcriptional network in the clinically relevant cell population of hESC-derived neural precursor cells (hESC-NPCs).

Specifically we will: 1) determine the function of MEF2C during in vitro neurogenesis (generation of new nerve cells) from hESC-NPCs; 2) investigate the therapeutic potential of MEF2C engineered hESC-NPCs in Parkinson's and stroke models; 3) determine the MEF2C DNA (gene) binding sites and perform a "network" analysis of MEF2C target genes in order to understand how MEF2C works in driving the formation of new nerve cells from hESCs.

Statement of Benefit to California:

Efficient and controlled neuronal differentiation from human embryonic stem cells (hESCs) is mandatory for developing future clinical cell-based therapies. Strategies to direct differentiation towards neuronal vs. glial fate are critical for the development of a uniform population of desired neuronal specificities (e.g., dopaminergic neurons for Parkinson's disease (PD)). Our laboratory was the first to clone and characterize the transcription factor MEF2C, the major isoform of MEF2 found in the developing brain. Based on our encouraging preliminary results that were obtained with mouse (m)ESC-derived and human fetal brain-derived neural precursors, we propose to investigate if MEF2C enhances neurogenesis from hESCs. In addition to neurogenic activity, we have shown that MEF2C exhibits an anti-apoptotic (that is, anti-death) effect and therefore increases cell survival. This dual function of MEF2C is extremely valuable for the purpose of transplantation of MEF2C-engineererd neural precursors. Additionally, we found MEF2 binding sites in the Nurr1 promoter region, which in the proper cell context, should enhance dopaminergic (DA) neuronal differentiation. We hypothesize that hESC-derived neural precursors engineered with MEF2C will selectively differentiate into neurons, which will be resistant to apoptotic death and not form tumors such as teratomas.

We believe that our proposed research will lead us to a better understanding of the role of MEF2C in hESC differentiation to neurons. These results will lead to novel and effective means to direct hESCs to become neurons and to resist cell death. This information will ultimately lead to novel, stem cell-based therapies to treat stroke and neurodegenerative diseases such as Parkinson's.

We also believe that an effective, straightforward, and broadly understandable way to describe the benefits to the citizens of the State of California that will flow from the stem cell research we propose to conduct is to couch the work in the familiar, everyday business concept of "Return on Investment." The novel therapies and reconstructions that will be developed and accomplished as a result of our research program and the many related programs that will follow will provide direct benefits to the health of California citizens. In addition, this program and its many complementary programs will generate potentially very large, tangible monetary benefits to the citizens of California. These financial benefits will derive directly from two sources. The first source will be the sale and licensing of the intellectual property rights that will accrue to the state and its citizens from this and the many other stem cell research programs that will be financed by CIRM. The second source will be the many different kinds of tax revenues that will be generated from the increased bio-science and bio-manufacturing businesses that will be attracted to California by the success of CIRM.
